Clinical Conference

Arsenic Poisoning

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine, Albuquerque. Taken from a transcription, it has been edited by Ralph C. Williams, Jr, MD, Professor and Chair of the Department of Medicine.

MICHAEL S. GORBY, MD*: This generation of clinicians is relatively unaware of the hazards of arsenicals. Advances in the treatment of syphilis and parasitism—which primarily used arsenicals—and in industrial and environmental public health have dramatically decreased clinicians' exposure to cases of arsenic toxicity. Unfortunately, the problem is still present, and it would be a mistake to assume it no longer exists. Arsenic is still the most common source of acute heavy metal or metalloid poisoning and is second only to lead with respect to chronic ingestion.[1] I have been involved in the care of two patients with arsenic poisoning in a span of eight months while at the Albuquerque Veterans Administration Medical Center. One was a fulminant and fatal case of acute poisoning after a disturbed 17-year-old woman intentionally ingested an arsenic trioxide-containing rodenticide. The other is a case of chronic arsenic poisoning from an as-yet-unidentified source resulting in several hospital admissions and many medical complications in a 64-year-old man. The clinical material presented herein is from the records of these two patients.

To understand arsenic in biology, one must first understand its chemistry. Arsenic is a member of the nitrogen family or group 5(a) of the periodic table of the elements. It has atomic number 33 with an atomic weight of 74.9 and is classified as a transition element or metalloid. This classification reflects the fact that arsenic commonly forms complexes with metals, but it also reacts readily to form covalent bonds with carbon, hydrogen, and oxygen. In fact, far more organic compounds of arsenic have been made than of any other trace element.[2] Arsenic may exist in three different oxidation or valence states, namely, the metalloid (0 oxidation state), arsenite (trivalent or +3 oxidation state), and arsenate (pentavalent or +5 oxidation state). Different arsenic-containing compounds vary substantially in their toxicity to mammals. Arsine gas (AsH_3) is clearly the most toxic, followed in order of generally decreasing toxicity by inorganic trivalent compounds, organic trivalent compounds, inorganic pentavalent compounds, organic pentavalent compounds, and, finally, elemental arsenic. Some arsenic compounds are apparently not toxic at any dose.[2] Toxicity also depends on other factors such as physical state—gas, solution, or powder—particle size, the rate of absorption into cells, the rate of elimination, the presence of impurities, and the nature of chemical substituents in the compound. Arsenicals are not cumulative in most mammals, and toxicity parallels excretion.[3] Arsine toxicity has been thoroughly reviewed, is associated with a unique and rapid hemolysis not occurring in other types of arsenic poisoning, and will not be discussed further in this review.[4]

Because of the complex chemistry of arsenic, it is difficult to discuss arsenic poisoning as a single clinical disorder. Critically evaluating published work on this topic is also hampered when it is not made clear what specific chemical compounds are discussed. The use of the blanket term, arsenic, is inappropriate. In this review I will concentrate on delineating the intriguing and important role this element has played throughout history and on the varied ways one may be exposed to arsenic. Brief discussions of the toxicity and biochemistry of arsenic and the clinical manifestations and treatment of arsenic poisoning will follow. Interested readers are referred to several excellent reviews on these matters.[3,5,6]

Sources of Exposure

Exposure to arsenic may come from natural sources, from industrial sources, or from intentionally administered sources, with either a benevolent or a malevolent intent.

Natural Sources

Arsenic is ubiquitously distributed in the environment. Sea water ordinarily contains 0.006 to 0.03 parts per million (ppm) of arsenic.[7] It is the 20th most common element in the earth's crust, although its concentration varies greatly.[8] In active geothermal areas, arsenic is naturally present in soil in amounts as high as 20 ppm, and levels of several hundred ppm may be found after years of spraying with pesticides.[9] Arsenic is present in all living organisms. The average daily human intake is 0.5 to 1 mg, most of which is in the form of food and water.[3] The highest concentrations are found in fish and crustaceans, and urinary arsenic concentrations can increase tenfold after a large seafood meal. The normal body burden in adults is approximately 20 mg.

Environmental arsenic mainly exists as sulfide complexes such as realgar (As_2S_2), or orpiment (As_2S_3) and iron pyrites (FeAsS) and is only occasionally found in its pure elemental

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(Gorby MS: Arsenic poisoning [Clinical Conference]. West J Med 1988 Sep; 149:308-315)

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state. The Arabic word for orpiment—a corruption of *auri pigmentum,* meaning "king's gold"—was *Az-zernikh,* and it is the probable root word of the present term. Arsenic ores are usually found in large concentrations in the presence of other metal ores, many of which are sought commercially. When heated to 193°C (379°F), arsenic sublimes from ores and oxidizes readily to trivalent As_2O_3. This is a fine granular white powder and is known as white arsenic, arsenic trioxide, or, for centuries, as simply arsenic. The ancients obtained "arsenic" in this manner by roasting arsenical ores in air and collecting the volatilized arsenic as arsenic trioxide. Therefore, human exposure to arsenic trioxide began with the first primitive smelter.[10]

Industrial Sources

Humans in their use of natural resources release arsenic into the air, water, and soil. Anthropogenic sources exceed natural sources by at least threefold in terms of quantities of arsenic released into the environment. Moreover, these sources are geographically confined and may present local environmental hazards. The main sources of anthropogenic arsenic release into the environment are through the smelters of the metal industry, fertilizer and pesticide spraying, and the burning of fossil fuels.[7]

Arsenical compounds have found use as the active ingredients in a number of commercial products. They are or have been used in wood preservatives, pesticides, herbicides, fungicides, cattle and sheep dips, desiccants, defoliants, dyestuffs, feed additives, drugs, and war gases. A number of miscellaneous uses include those such as a glass clarifier, an important element in the electronics industry, and as an additive that increases hardening and heat resistance of metal alloys. The use of arsenic in many of these areas followed the development of the industrial revolution as a consequence of being an inexpensive by-product of the smelting of nonferrous metals such as copper, iron, zinc, gold, and other metals. Arsenic's commercial uses peaked in the late 1960s and have been steadily declining in most areas. Exceptions to this decline are the use of arsenic in the electronics industry and as a wood preservative in conjunction with copper and chromium. Although arsenicals remain the best agents for certain applications in agriculture, their usage in insecticides and herbicides has largely been replaced by hydrocarbon products. Today less than 30,000 tons of arsenic trioxide is manufactured secondarily in world production.[11] About 97% of the arsenic produced enters end-product manufacture in the form of white arsenic, the remaining 3% as metal for metallurgic additives. The only United States plant recovering arsenic from metal ores is a copper smelter in Tacoma, Washington. Present US markets for arsenic trioxide are shown in Figure 1.

Occupational and environmental health problems can result from the ubiquitous commercial presence of arsenicals. To paraphrase the title of a well-known play, this may be a problem of "arsenic and old waste." The National Institute of Occupational Safety and Health estimates that 1½ million people are potentially exposed to arsenic during the course of their work.[12] Smelter workers appear to have an increased mortality—primarily from lung cancer—proportional to their arsenic exposure.[13] Large-scale accidental arsenic poisonings have occurred in the past. At the turn of this century, more than 6,000 British beer drinkers were apparently poisoned with arsenic in the well-known "Staffordshire beer epidemic." This was a manufacturing mishap in the Manchester area of England traced primarily to arsenic in iron pyrites used to make sulphuric acid that, in turn, was used to make the glucose for brewing. Although some have incriminated selenium in this epidemic, it provided the impetus for the first government-mandated industrial regulations for arsenic.[2] In 1955 more than 12,000 Japanese infants were poisoned, causing 130 deaths, when the sodium phosphate used as a stabilizer in infant formula preparations was found to be contaminated with arsenic.[7] More recently, 11 cases of arsenic poisoning in a western Minnesota community were attributed to the consumption of well water contaminated from an adjacent arsenical insecticide storage dump.[9] There is also a report of probable arsenic poisoning of a family in rural Wisconsin from extensive burning of marine plywood—treated with chromium-copper-arsenate—in a poorly ventilated cabin.[14]

Administered Sources

Arsenic has been used as a medicine and as a poison since humans first became interested in chemistry.

Malevolent intent. Arsenic probably has the worst public relations record of any element, and its name has become almost synonymous with the term poison. The popularity of arsenic as a poison is due more to its availability, inexpensiveness, and the fact that it is tasteless and odorless than to its extreme toxicity. Common arsenicals simply are not that efficient as a poison, leading to a slow and painful, not instantaneous, death. In his play *Arsenic and Old Lace,* John Kesselring was careful to include cyanide and strychnine in the concoction with which the little old ladies swiftly and unerringly dispatched their gentleman callers. Arsenic simply would not have done it alone, yet it made a far more intriguing title.

Aristotle and Socrates had known a few vegetable poisons such as hemlock and henbane. They were most familiar, however, with the inorganic poison arsenic trioxide that, in

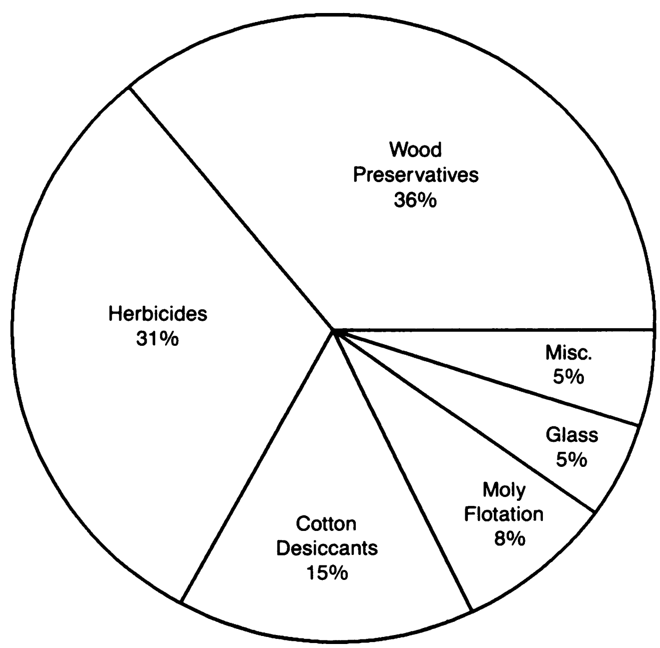

Figure 1.—The figure shows the United States markets for arsenic trioxide estimated by the American Smelting and Refining Company.[11]

TABLE 1.—*Poisoning Attempts in 19th Century France per 1,000**

Arsenic	331	Opiates	12
Phosphorus	301	Mercurials	9
Copper	183	Antimonials	6
Mineral acids	54	Cyanides	5
Cantharides	35	Iron	5
Strychnine	14	Other	45

*Reported in 1885 by Blyth.[16]

the course of the following centuries, became the poison of poisons. One of the earliest documented cases of arsenic poisoning was Nero's poisoning of Britannicus to secure his Roman throne in the year 55 AD. The poisoner became an integral part of social and political life in the early Middle Ages—arsenic was known to be the favorite of some. The records of the city councils of Florence and Venice contain ample testimony of the political use of poisons. Contracts were recorded, naming victims and prices, and when the deed was accomplished, the notation "factum" would be entered into the city archives.[15] Poisoners like the Borgia pope, Alexander VI, and his son, Cesare Borgia, became legendary, as did such sinister figures as Teofania di Adamo and Marie Madeleine, who in the 17th century killed left and right with arsenic solutions. White arsenic acquired so terrible a reputation that ultimately it was called *poudre de succession,* "inheritance powder." Arsenic was the favorite poison of 19th century France, as recorded by early forensic toxicologists (Table 1).[16] A French woman named Catherine Deshayes commercialized this service, which grew to infamous proportions, earning her the title, "La Vosine." Her business dissolved with her execution when a special judicial commission established by Louis XIV convicted her of many poisonings, including more than 2,000 infant victims.[15]

Poisoning seems to have been accepted as one of the normal hazards of daily life in this era. Devices and methods of poisoning proliferated at an alarming rate. Arsenic's popularity as a poison, however, declined dramatically in the latter half of the 19th century, at least partly due to the development of a highly reliable and sensitive assay for arsenic described by Marsh in 1836.[17] The importance of this test can be appreciated from its use as decisive evidence in the trial of a celebrated poisoner, Marie Lafarge, for the murder of her husband in 1842.[17] Variations of this test that involve acidifying body tissue or fluids and detecting liberated arsine gas colorimetrically are still in use today as qualitative diagnostic tests (Reinsch's test, Gutzeit's test).

Two rather notable case histories of arsenic exposure with malevolent intent have appeared in the scientific literature recently. These cases illustrate some of the power and pitfalls of the forensic toxicology of arsenic. The first is that of Charles Francis Hall, a Cincinnati printer and businessman who, at the age of 37, felt a messianic calling to explore the North Pole. He left family, home, and business and became one the of the best and most daring of Arctic explorers. In 1871 he headed the US North Polar Expedition and pushed his ship, Polaris, through ice-choked seas to the very northern tip of Greenland and planned to winter there. The crew had other ideas. They were hostile and afraid, but Hall ignored them, making frequent solo sojourns into the surrounding vastness. He returned one night, in the darkness and cold, drank a cup of black coffee, and became violently ill, experiencing a seizure. He rallied, lived for two weeks, then died and was buried in a two-foot deep grave in the permafrost. Nearly a century later, adventuresome researchers located the grave and did an autopsy that included neutron activation analysis of fingernails and hair samples.[18] This revealed "an intake of considerable amounts of arsenic by C. F. Hall in the last two weeks of his life."

A second case involves an interesting debate in the scientific and popular literature on how to account for elevated concentrations of arsenic in specimens of hair preserved from the scalp of Napoleon Bonaparte, who died in 1821. Theories to explain these arsenic levels abound and include the work of secret assassins, long-term ingestion by the deposed emperor in the paranoid belief it would protect him from attempted poisonings, and administered therapies for illness. The best accepted explanation appears to be that it came from his wallpaper! The green copper arsenite pigments (Scheele's green and Paris green) were introduced in about 1780 and were soon widely used in paints and wallpapers. On damp wallpaper, many molds can metabolize arsenic compounds to volatile, poisonous trimethylarsine, which is released into the air in the room. Throughout the 19th century, many people were made ill or even killed in this manner.[19] When researchers analyzed an original sample of wallpaper from Napoleon's residence on Saint Helena, they found enough arsenic to be capable of causing illness but probably not death.[20]

Benevolent intent. The medicinal effects of arsenicals were written about by Hippocrates (460-357 BC), Aristotle (384-322 BC), and Pliny the Elder (23-79 AD). Hippocrates had administered orpiment and realgar as escharotics and as remedies for ulcers. Paracelsus (1493-1541), one of the strangest and most paradoxic characters in medical history, is known to have used elemental arsenic and mercury extensively. He formulated many then-revolutionary views that remain an integral part of the structure of toxicology. He promoted a focus on "the toxicon," the toxic agent, as a chemical entity. A pertinent remark attributed to Paracelsus is that "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."[15] Small doses of inorganic arsenicals have long been felt to have a "tonic" or "alterative" property, which led to their enthusiastic use for more than two centuries. Initially these compounds cause a cutaneous capillary flush, giving a "milk and roses" complexion enjoyed by many women. Local mountaineers in Austria, the so-called arsenic eaters, have consumed large quantities of arsenical ores in the belief it improves endurance at high altitudes, increases weight, strength, and appetite, and clears the complexion.[10] Taken internally in either liquid or solid form, injected hypodermically, inhaled as a vapor, administered intravenously, and, on rare occasions, even given in enemas, arsenic proved to be one of the mainstays of the 19th century *materia medica.*[21] Many arsenic-containing "medicinals"—Fowler's solution, Asiatic pills, Donovan's solution, DeValagin's elixir, to name but a few—came into use for a variety of ailments. These were considered at various times specific therapy for anorexia and other nutritional disturbances, neuralgia, rheumatism, asthma, chorea, tuberculosis, diabetes, intermittent fever, skin disorders, and hematologic abnormalities. Perhaps the most widely prescribed of these agents was Fowler's solution, a 1% potassium arsenite concoction introduced by Thomas Fowler in the London Pharmacopoeia in 1809. It was withdrawn from the US market in the 1950s after several case series linking its prolonged use to skin changes, cutaneous malignant lesions, and neuropathies appeared. Arsenic retains its mystique as a panacea in many cultures. At the popular hot springs in Ojo Caliente, New Mexico, visitors receive a pamphlet, "The Doorway to Better Health," attesting to the benefits of using arsenic. It reads, "To achieve the best results, it is suggested to drink the pleasant tasting waters, as well as to bathe in them. . . . The *arsenic* water is the only known water of its kind in this country. Arsenic is a most powerful healing element."

By the early 1900s, physicians began using the less toxic organic preparations of arsenic—sodium cacodylate and sodium arsanilate—for the treatment of pellagra, as well as for malaria and sleeping sickness. In 1909, Ehrlich's experiments with arsenic led to the widespread use of arsphenamine (salvarsan), often called "606," which, until its replacement by penicillin, was the principal drug in the treament of syphilis for nearly 40 years. Its success stimulated intense activity on the part of the organic chemists who extended the list of synthesized arsenic compounds from 606 to an estimated 32,000.[3] Arsenicals in medicine are now largely replaced by antibiotics but are still used as antiparasitic agents in veterinary medicine and occasionally in patients with trypanosomiasis and amebiasis.

Toxicity and Biochemistry

Much of the basis of our current understanding of the mechanism of arsenic toxicity in living systems comes from work on arsenic toxicity in animals in the late 1800s, from the development of organic arsenical drugs during the early 1900s, and from work stimulated during the 1940s by the need to find effective antidotes for arsenical warfare agents. The difference in toxicity between trivalent and pentavalent arsenic compounds can best be understood by considering the biochemical mechanism of action of these two distinct families of compounds. Present knowledge concerning the biochemical mechanisms of arsenic toxicity in mammals is far from complete, although some aspects of this problem have been studied in considerable detail. Single cell studies have established that specific forms of arsenic can be cytotoxic, and it is generally thought that the overt toxicity of arsenic is due to the inhibition of critical sulfhydryl-containing enzymes by trivalent arsenic.[6] Many enzymes are susceptible to deactivation by arsenic. In most cases the enzyme activity can be restored by adding an excess of a monothiol such as glutathione, suggesting that the inhibition is due to the reaction of the arsenic with a single sulfhydryl group in the enzyme molecule. An important exception to this generalization, however, proved to be the pyruvate oxidase system, which could not be protected against trivalent arsenicals by even a 200% excess of monothiol. Such an apparent anomaly was clarified when it was shown that arsenicals can complex with two sulfhydryl groups in the same protein molecule, thereby forming a stable ring structure that is not easily ruptured by monothiols. This finding stimulated the testing of various dithiol compounds for their ability to block the action of arsenicals on pyruvate oxidase and led to the discovery of 2,3-dimercaptopropanol, also known as British antilewisite. This agent eventually became a widely used antidote for arsenic poisoning, allowing the formation of a stable, soluble five-membered ring that is excreted in the urine (Figure 2).

The simultaneous interaction of arsenic with two thiol groups led Peters to postulate the existence of a dithiol-containing cofactor in the pyruvate oxidase system.[22] This idea was later verified with the identification of lipoic acid. The pyruvate oxidase complex is necessary for oxidative decarboxylation of pyruvate to acetyl coenzyme A and carbon dioxide before it enters the tricarboxylic acid cycle. This enzyme system comprises several enzymes and cofactors. In the presence of trivalent arsenic, a dihydrolipoyl-arsenite chelate is formed, preventing the reoxidation of the dihydrolipoyl group necessary for continued enzymatic activity, and this pivotal enzyme step is shut down.[23] It is also apparent that some cellular effects of thiamine deficiency are identical to arsenic poisoning and may explain their similar clinical manifestations (Figure 3).[24]

These well-defined cellular effects of trivalent arsenic may be modified in more complex systems by in vivo oxidation-reduction reactions, differences in uptake and loss from particular organ systems, and by differences in the natural susceptibility of various tissues. Little is known about the biotransformation of arsenicals in humans. Some pentavalent compounds are partly reduced in vivo to the more toxic trivalent forms, but the redox equilibrium in vivo favors the pentavalent state.[6] Although pentavalent arsenic does not appear to lead to enzyme inhibition, it cannot be dismissed as nontoxic because of its potential to uncouple oxidative phosphorylation. The mechanism is thought to be related to the competitive substitution of arsenate for phosphate, with which it is isoelectric and isosteric, with the subsequent formation of an unstable arsenate ester bond that is rapidly hydrolized. Thus, the so-called high-energy bonds of adenosine triphosphate are not conserved in the presence of arsenate.[3] This process is termed arsenolysis. Arsenic may therefore be doubly toxic to cells by inhibiting energy-linked

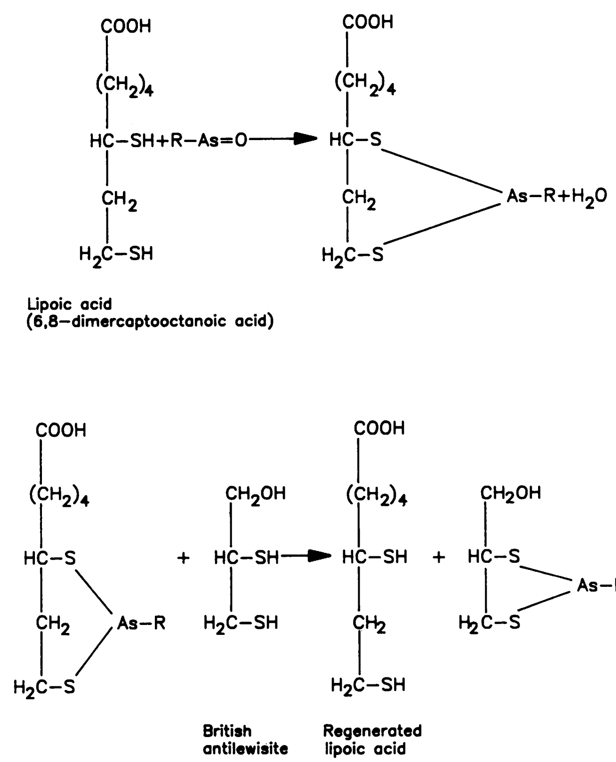

Figure 2.—Lipoic acid reacts with a trivalent monosubstituted arsenical and is regenerated by adding British antilewisite.

functions of the mitochondria in two very different ways. Trivalent arsenic inhibits the reduction of nicotinamide adenine dinucleotide by deactivating critical enzymes in the tricarboxylic acid cycle, and pentavalent arsenic uncouples oxidative phosphorylation by arsenolysis.

Soluble forms of arsenic are nearly completely absorbed from the gastrointestinal or respiratory tract and probably also from the skin. Excretion is primarily through the urine in the form of methylated arsenic, although the organic arsenic in seafood is largely excreted unchanged.[25] Absorbed arsenic is initially bound to the protein portion of hemoglobin, yet leaves the intravascular space within 24 hours and is concentrated in the liver, kidneys, spleen, lungs, and gastrointestinal tract. After two to four weeks, most arsenic remaining in the body is found in hair, nails, and skin due to the high sulfhydryl content of keratin and is slowly excreted in this manner. Renal dysfunction is a major impediment to the normal excretion of all arsenic compounds.

Clinical Manifestations

The clinical manifestations of arsenic poisoning depend on the type of arsenical involved and on the time-dose relationship of exposure. A fatal dose of arsenic trioxide is probably in the 200- to 300-mg range, yet a dose of 20 mg has been life-threatening, and recovery from 10 grams has occurred.[5] Clinical manifestations may conveniently, although somewhat artificially, be described as either acute or chronic (Table 2).

Acute Poisoning

Symptoms of acute intoxication usually occur within 30 minutes of exposure. Initially a patient may have a metallic taste or notice a slight garlicky odor to the breath, associated with a dry mouth and dysphagia. Severe nausea and vomiting, colicky abdominal pain, and profuse diarrhea with rice-water stools abruptly ensue. In acute arsenic poisoning of massive proportions, almost always as an attempt at suicide, the fundamental lesion of endothelial cellular toxicity can be considered to account for the predominant clinical features. Capillary damage leads to generalized vasodilation, transudation of plasma, and shock. Arsenic's effect on the mucosal vascular supply, not a direct corrosive action, leads to transudation of fluid into the bowel lumen, mucosal vesical formation, and sloughing of tissue fragments. Cyanosis, hypoxic encephalopathy and seizures, acute tubular necrosis, and death may occur due to hypovolemia.

TABLE 2.—*Clinicopathologic Findings in Acute and Chronic Arsenic Poisoning*

System	*Acute*	*Chronic*
Skin	Hair: delayed loss; nails: Mees's lines (2-3 weeks postingestion)	Melanosis, Bowen's disease, facial edema, hyperkeratosis, cutaneous cancers, hyperpigmentation
Neurologic	Hyperpyrexia, convulsions, tremor, coma	Encephalopathy, polyneuropathy, tremor, axonal degeneration
Gastrointestinal tract	Abdominal pain, dysphagia, vomiting, bloody or rice-water diarrhea, mucosal erosions	Nausea, vomiting, diarrhea; anorexia, weight loss
Liver	Fatty infiltration	Hepatomegaly, jaundice, cirrhosis
Kidney	Tubular and glomerular damage—oliguria, uremia	Nephritic findings
Hematologic		Bone marrow hypoplasia; anemia, leukopenia, thrombocytopenia; impaired folate metabolism; basophilic stippling and karyorrhexis
Cardiac	ST-T wave abnormalities, prolonged QT interval, ventricular fibrillation, atypical ventricular tachycardia	...

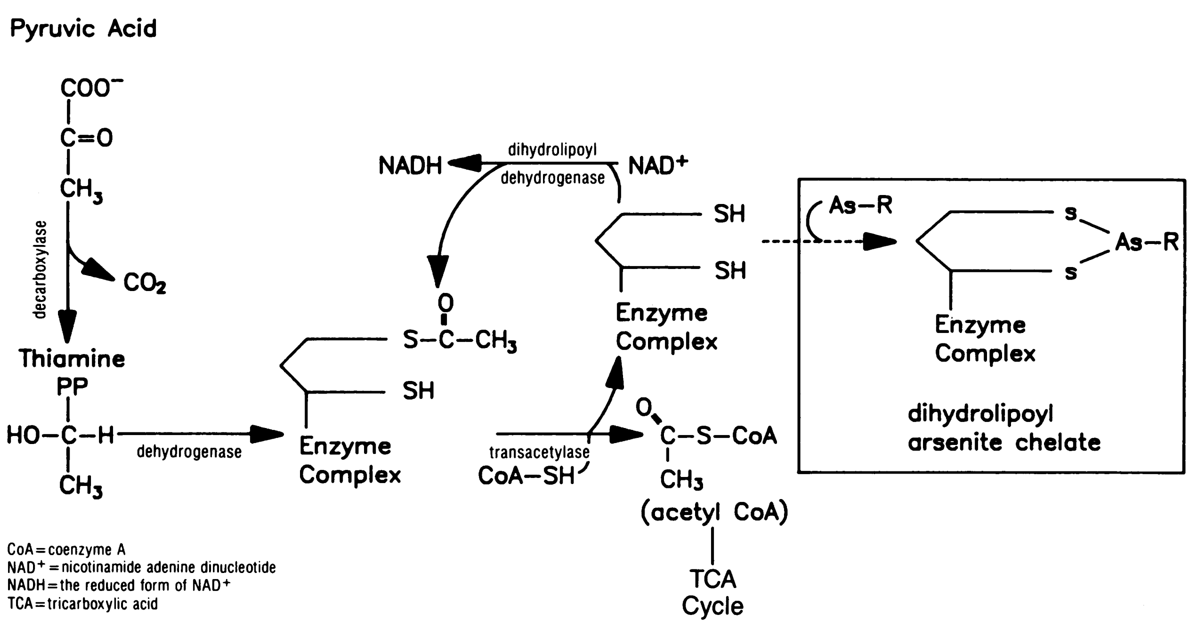

Figure 3.—The effect of trivalent arsenic on sulfhydryl enzyme systems: Shown here is the inhibition of pyruvate oxidase by the formation of an arsenite chelate preventing reoxidation of the dihydrolipoyl group necessary for continued enzymatic activity. Succinate oxidation is disrupted in an identical manner, as are many other enzymes.

Following the gastrointestinal phase, multisystem organ damage may occur. If death does not occur in the first few hours from irreversible circulatory insufficiency, it may result from hepatic or renal failure over the next several days. Cardiac manifestations include acute cardiomyopathy, subendocardial hemorrhages, and electrocardiographic changes. The most common changes on an electrocardiogram are prolonged QT intervals and nonspecific ST-segment changes.[26] A case of an atypical ventricular fibrillation resembling torsades de pointes has been reported.[27] The pathologic lesions described in patients with rapidly fatal arsenic intoxication are fatty degeneration of the liver (Figure 4), hyperemia and hemorrhages of intestine (Figure 5), renal tubular necrosis, and demyelination of peripheral nerves.

Chronic Poisoning

Chronic arsenic poisoning is much more insidious in nature, often with multiple hospital admissions before the correct diagnosis is made. The source of arsenic exposure is discovered in less than 50% of cases. There are several good reviews of arsenic's effects on various organ systems.[3,10] I will mention only briefly the most prominent chronic manifestations involving the skin, blood, and neurologic systems.

The cutaneous changes are characteristic yet nonspecific. An initial persistent erythematous flush slowly leads to melanosis, hyperkeratosis, and desquamation. The skin pigmentation is patchy and has been given the poetic description of "raindrops on a dusty road." The hyperkeratosis is frequently punctate and occurs on the distal extremities. A diffuse desquamation of the palms and soles is also seen. Long-term cutaneous complications include the development of Bowen's disease and multiple cutaneous malignant tumors.[28] Brittle nails, patchy alopecia, and facial edema can occur. Transverse white bands across the nails (Aldrich-Mees's lines) are frequently seen three to four weeks after an acute exposure and may even be used to date the event.

Anemia and leukopenia are almost universal with chronic arsenic exposure; thrombocytopenia frequently occurs. The anemia is usually normochromic and normocytic and caused at least partially by hemolysis.[29] Interference with folate metabolism and DNA synthesis may result in megaloblastic changes.[30] Karyorrhexis, an accelerated pyknosis of the normoblast nucleus, is characteristic of arsenic poisoning. This is manifested as bizarre nuclear forms seen on bone marrow examination (Figure 6). Basophilic stippling is also seen. Aplastic anemia progressing to acute myelogenous leukemia has been reported.[31]

A peripheral neuropathy is the hallmark of chronic arsenic poisoning but may be seen within two hours of ingestion. Usually it is a symmetric polyneuropathy of both sensory and motor nerve fibers, often resembling the Landry-Guillain-Barré syndrome in its presentation.[32] On microscopic examination, there are resorption of myelin and destruction of axonal cylinders progressing to nerve atrophy and perineural fibrosis (Figure 7).

Treatment of Arsenic Poisoning

In patients with acute arsenic poisoning, supportive therapy and chelation treatment are indicated. Essential supportive measures, as with any poisoning, include scrupulous intestinal decontamination—charcoal lavage and the administration of cathartics—and adequate intravenous fluid therapy. Exchange transfusions may be of help in clearing the blood of elevated arsenic concentrations early in the course. Hemodialysis may be a useful adjunct in treating a patient with acute arsenic poisoning with concomitant renal failure.[33]

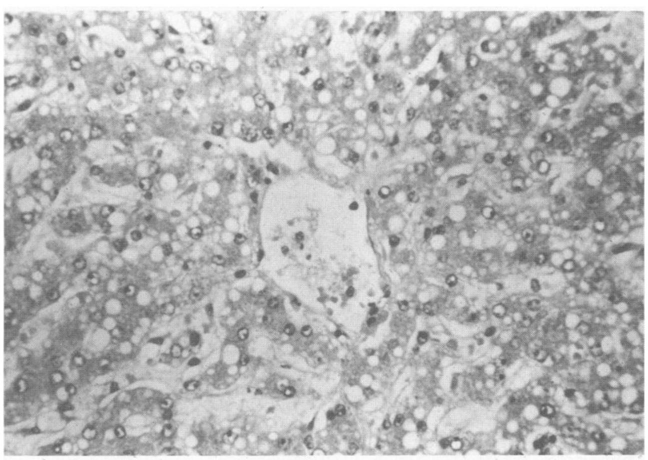

Figure 4.—The photomicrograph of liver shows acute fatty change from a patient dying 12 days after a massive (more than 7 grams) overdose of arsenic trioxide (original magnification × 40).

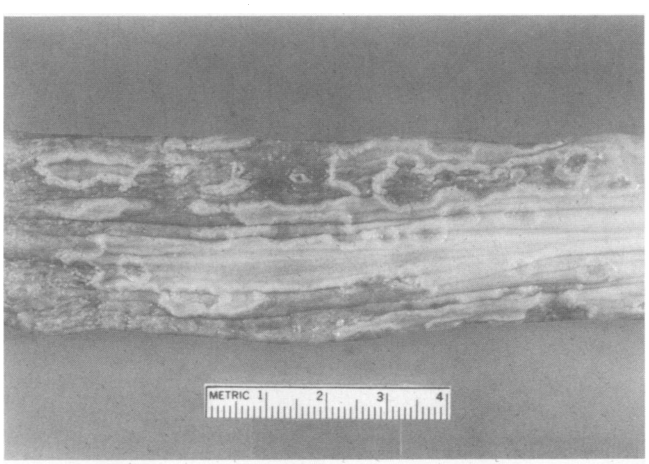

Figure 5.—The photograph shows the gross specimen of distal esophagus from the same patient as in Figure 4. Necrotic oral lesions and pronounced hemorrhagic gastritis were also noted.

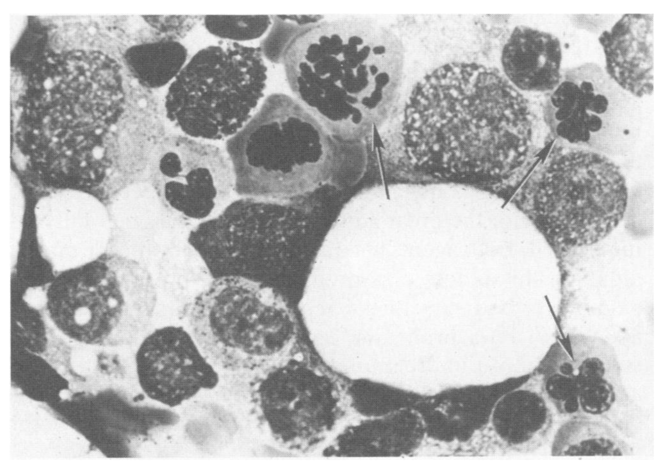

Figure 6.—The photomicrograph is of a bone marrow specimen from a 64-year-old man with chronic arsenic poisoning. Most notable are bizarre nuclei in the erythrocytic precursors—karyorrhexis—indicated by arrows (original magnification × 100).

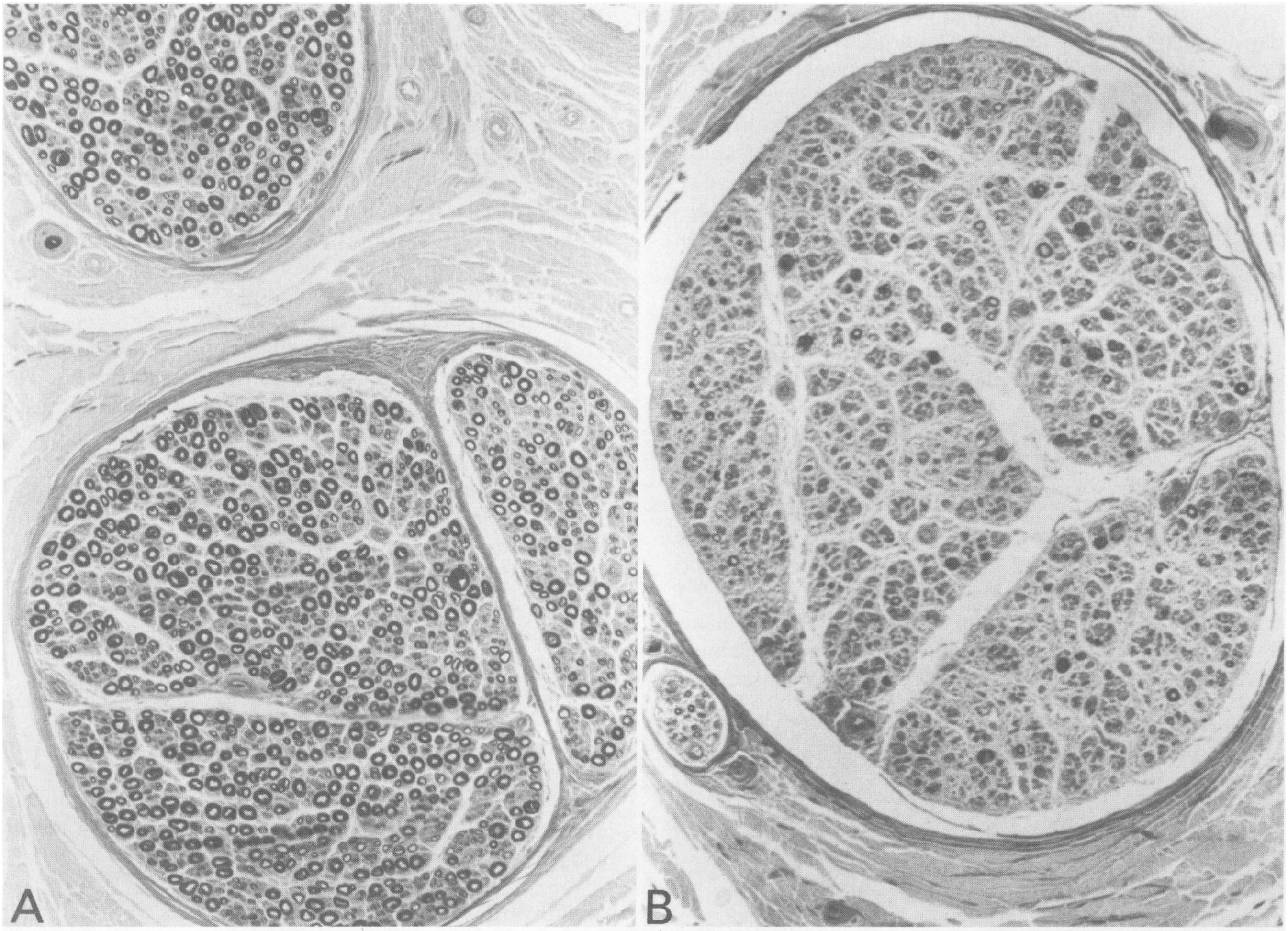

Figure 7.—The photomicrographs of osmium-stained sections of sural nerves show **(A)** a normal specimen taken at autopsy and **(B)** a surgical specimen from the same patient as in Figure 6. A loss of the myelin sheath—normally stained by osmium—and perineural fibrosis can be seen (original magnification × 20).

Dimercaprol (2,3-dimercaptopropanol) is the traditional chelating agent used, but penicillamine has been used with some success.[34] Parenteral dimercaprol is administered intramuscularly at the initial dose of 3 to 5 mg per kg of body weight every four hours. The dose should be tapered but administration continued until the urinary arsenic excretion is less than 50 μg per 24 hours. This therapy is frequently effective in preventing or neutralizing systemic toxicity. In most cases the degree of recovery from neuropathy, aplastic anemia, encephalopathy, and jaundice is limited and directly related to the initial severity of the systemic involvement and the rapidity with which chelation therapy is initiated. Penicillamine, although only a monothiol agent, has been used successfully with the great advantage that it may be orally administered. Both agents have a high frequency of side effects, although this is less of a problem in the presence of large amounts of body arsenic. A recently reintroduced drug that appears to be a promising agent for treating arsenic poisoning is 2,3-dimercaptosuccinic acid. This is a dithiol agent, can be orally administered, and has few reported side effects.[35] Experience, however, is limited with the use of this drug.

Chronic arsenic poisoning can also be treated with chelating agents, but the possible benefits must be weighed against the known side effects. There is little convincing evidence of the benefit of chelation therapy in most cases of chronic poisoning.

Summary

Arsenic is a metalloid that has played an important and fascinating role throughout recorded history. Exposure to toxic amounts of arsenic continues to occur in this country. Certain aspects of the metabolism and biochemistry of the arsenical compounds are now well understood, and the application of this knowledge has led to a rational basis of therapy for cases of acute poisoning. The clinical manifestations of arsenic poisoning are myriad, and the correct diagnosis depends largely on being aware of the problem.

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Urgency Incontinence in Children

STRESS INCONTINENCE IS NOT AN ENTITY WE GENERALLY RECOGNIZE IN THE PEDIATRIC POPULATION. Stress incontinence is incontinence with laughing, coughing, or lifting, and that's usually something we think of in older persons—the multiparous woman; the man with some prostatism or after prostatic surgery.

What we usually see in children is urgency incontinence, and that's entirely different. That's these uninhibited bladder contractions. There is a group of patients, generally adolescent girls, who have "giggle" incontinence. "Giggle" incontinence is one of the biggest pains in pediatric urology because it is untreatable. It is absolutely untreatable. These girls will be in a school situation with their friends, and you know how young girls are. They'll start talking, and suddenly someone will say "BOO," and they'll all explode in laughter . . . and one girl explodes from both ends. She's just sitting in a puddle of urine, and it's very embarrassing.

I've tried using an anti-cholinergic. I've tried exercises. I've sent some of them to the behavior-modification people at Johns Hopkins who are interested in this. In my youth, I even operated on one of these children, which I will never do again. It's untreatable. All you can do is try to get them to change their laugh pattern. And it's also unexplainable to me. I really do not understand what happens with "giggle" incontinence, but the only thing I suggest to them is, make sure that, before they stand in the corner with their girlfriends, they go to the toilet. At least if they're going to lose their urine, they'll lose less. Also, they should try not to explode with laughter. Well, you know, you hate to see a young girl not being able to giggle. That's a real problem.

—A. BARRY BELMAN, MD

Extracted from *Audio-Digest Pediatrics*, Vol. 34, No. 9, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206